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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/848,990	SHAN ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *14-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's claim for domestic priority to provisional application Serial No. 60/201,601 under 35 U.S.C. 119(e) is acknowledged.

Applicant's preliminary amendment submitted October 19, 2001 is acknowledged, wherein the instant specification has been amended as to page 2, the paragraph at line 13 of page 5 and the paragraph at line 20 of page 6.

Election/Restrictions

Applicant's election with traverse of the invention of Group I, Claims 1-13 and 34-41 drawn to methods for modulating expression of a mammalian SREBP-1 gene in a cell and for ameliorating a condition associated with abnormal SREBP-1 expression in a mammal, submitted June 28, 2004, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

On consideration by the examiner, the specie election requirement dated January 22, 2004, is withdrawn.

Claims 1-13 and 34-41 will be examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 and 34-41 are rejected under 35 U.S.C. 112, first paragraph, for **scope** of enablement because the specification, while being enabling for a method for treating the specific and particular disorders/diseases such as hypertriglyceridemia by inhibiting expression of a mammalian SREBP-1 gene disclosed in the specification, does not reasonably provide enablement for any modulating expression and mediated expression which may encompass both enhancing or promoting, and inhibiting or reducing expression of a mammalian SREBP-1 gene. These actions are in opposite directions.

Note that the specifically therapeutic goal or the specifically therapeutic treatment of the claimed methods herein is lacking or absent.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The instant invention pertains to the methods for modulating expression and mediated expression, encompassing both enhancing or promoting, and inhibiting or reducing expression of a mammalian SREBP-1 gene, by administering the very same compound.

The state of the prior art: The skilled artisan would view that both enhancing or promoting, and inhibiting or reducing expression of a mammalian SREBP-1 gene, by administering the very same compound in a same mammal at the same time, is highly unlikely.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or lack thereof in the art: The skilled artisan would view that, both enhancing or promoting, and inhibiting or reducing expression of a mammalian SREBP-1 gene, by administering the very same compound in a same mammal at the same time, is highly unpredictable since the skilled artisan would not understand how the same compound or agent could enhance and inhibit expression of a mammalian SREBP-1 gene, by administering the very same compound in a same mammal at the same time.

The presence or absence of working examples: In the instant case, **no** working examples are presented in the specification as filed showing how to use the same compound herein to enhance or promote, and inhibit or reduce expression of a mammalian SREBP-1 gene.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to achieve methods of modulating expression and mediating expression of a mammalian SREBP-1 gene, by administering the very same compound, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-13, and 34-41 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular LXR-α antagonists such as 24,25-epoxycholerterol in the specification and claim 4 employed in the claimed methods herein for treating the particular disorders or diseases, does not reasonably provide enablement for the employment any "compound that promotes or inhibits LXRα -mediated expression of the SREBP-1 gene to a cell that

comprises an SREBP-1 gene and an LXRα polypeptide" for the claimed methods fo treatment herein.

These recitation, "compound that promotes or inhibits LXRα -mediated expression of the SREBP-1 gene to a cell that comprises an SREBP-1 gene and an LXRα polypeptide" is merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to methods herein for raising the plasma level of HDL in a mammal.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims 1-2 are deemed very broad since these claims may reasonably encompass not only those known but also unknown "compound that promotes or inhibits LXRα -mediated expression of the SREBP-1 gene to a cell that comprises an SREBP-1 gene and an LXRα polypeptide" as of the instant filing date,

even those future known compounds, employed in the claimed methods of treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "compound that promotes or inhibits LXRα -mediated expression of the SREBP-1 gene to a cell that comprises an SREBP-1 gene and an LXRα polypeptide" recited in the instant claims is purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides the particular compound such as oxysterols or 24,25-epoxycholerterol having the functional properties for the claimed method of treatment herein.

Thus, the instant specification fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph, since it fails to provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treatment for raising the plasma level of HDL in a mammal, side effects, and especially serious toxicity that may be generated by drug-

drug interactions when and/or after administering to a host (e.g., a human) any compounds represented by "that promotes or inhibits LXRα -mediated expression of the SREBP-1 gene to a cell that comprises an SREBP-1 gene and an LXRα polypeptide". See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except exysterols in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

Further, these recitations may broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date, as discussed

above. These recitations broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known compounds encompassed by claim 1 herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only several particular instant compounds were tested in the working examples herein (see Example at page 33-43 of the specification). Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the compounds encompassed in the claimed methods. See MPEP § 716.02(d).

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 5-13, and 34-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Medina et al. (WO 99/10320, PTO-892).

Medina et al. discloses that the structural formula I therein are are useful in a composition and in a method of treatment of hypercholesterolemia, hyperlipoproteinemia or atherosclerosis in a mammal. See in Medina et al. abstract. Medina et al. also teaches that the hyperlipoproteinemias result in elevations of cholesterol, triglycerides or both, and contribute to atherosclerotic diseases (see page 1, the 3rd paragraph). Medina et al. also discloses that administration of the active

compounds therein alone or in combination with a hypolipidemic agent or hypocholesterolemic agent to a mammal including human and the oral administration of the composition therein (see page 32-33. See in Medina et al. abstract, page 3 last paragraph, page 6 lines 6-7 and 12-13, page 7, page 32-33, and claims 95-111, 119, and 120.

Medina's method inherently treats hypertriglyceridemia, as claimed herein since Medina's method steps are same as the instant method steps. See *Ex parte Novitski*, 26 USPQ 2d 1389. Additionally, it is well known a patient having diabetes mellitus, i.e. insulin resistance and an elevated plasma insulin level, also suffering from hypercholesterolemia or hyperlipidemia or hypertriglyceridemia.

Thus, Medina et al.anticipates claims 1-3, 5-13, and 34-41.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Dollis et al. ("*Effects of a 2,3-oxidosqualene-lanosterol cyclase inhibitor, 2,3: 22,23-dioxidosqualene and 24,25-epoxycholesterol on the regulation of cholesterol biosynthesis in human hepatoma cell line HepG2*", PTO-892).

Dollis et al. discloses that 24,25-epoxycholesterol is an inhibitor of cholesterol biosynthesis in human hepatoma HepG2 cells by administering 24,25-epoxycholesterol to a cell herein. Thus, Dollis et al. anticipates claims 1-7, since Dollis's method steps are same as the instant method steps. See *Ex parte Novitski*, 26 USPQ 2d 1389.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Sato et al. ("*Oxygenated sterols as inhibitors of enzymic conversion of dihydrolanosterol into cholesterol*", PTO-892).

Sato et al. discloses that (24S)-24,25- epoxycholesterol and (24R)-24,25-epoxycholesterol, (22S)-22-hydroxycholesterol, are an inhibitor of cholesterol biosynthesis in rat liver cells by administering 24,25-epoxycholesterol to a cell herein. Thus, Dollis et al. anticipates claims 1-7, since Sato's method steps are same as the instant method steps. See *Ex parte Novitski*, 26 USPQ 2d 1389.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5-13, and 34-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39-42 of U.S. Patent No. 6,316,503.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent are drawn to a method of modulating LXR function

in a cell, tissue, or animal, and/or wherein said LXR function is associated with a disease or condition selected from the group of lipid disorders and other metabolic disorders, comprising administering the instant compound and/or in combination with a second lipid-lowering agent or cholesterol-lowing agent.

The claim of the instant application is drawn to methods for modulating expression of a mammalian SREBP-1 gene comprising administering the same compound having the same functions.

Thus, these methods between in the patent and in the instant application are seen to substantially overlap. Therefore, the instant claims 1-3, 5-13, and 34-41 are seen to be anticipated by the claims 39-42 of U.S. Patent No. 6,316,503.

Claims 1-3, 5-13, and 34-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 17, and 25-27 of U.S. Patent No. 6,388,231.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent are drawn to a method of treating a disease state characterized by abnormally high levels of low density lipoprotein particles or cholesterol in the blood such as hypercholesterolemia comprising administering the instant compound and/or in combination with a second lipid-lowering agent or cholesterol-lowing agent.

The claim of the instant application is drawn to methods for modulating expression of a mammalian SREBP-1 gene comprising administering the same compound having the same functions.

Thus, these methods between in the patent and in the instant application are seen to substantially overlap. Therefore, the instant claims 1-3, 5-13, and 34-41 are seen to be anticipated by the claims 1, 17, and 25-27 of U.S. Patent No. 6,388,231.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
September 14, 2004